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Rapid Cortical Oscillations and Early Motor Activity in Premature Human Neonate

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Delta-brush is the dominant pattern of rapid oscillatory activity (8–25 Hz) in the human cortex during the third trimester of gestation. Here, we studied the relationship between delta-brushes in the somatosensory cortex and spontaneous movements of premature human neonates of 29–31 weeks postconceptional age using a combination of scalp electroencephalography and monitoring of motor activity. We found that sporadic hand and foot movements heralded the appearance of delta-brushes in the corresponding areas of the cortex (lateral and medial regions of the contralateral central cortex, respectively). Direct hand and foot stimulation also reliably evoked delta-brushes in the same areas. These results suggest that sensory feedback from spontaneous fetal movements triggers delta-brush oscillations in the central cortex in a somatotopic manner. We propose that in the human fetus in utero, before the brain starts to receive elaborated sensory input from the external world, spontaneous fetal movements provide sensory stimulation and drive delta-brush oscillations in the developing somatosensory cortex contributing to the formation of cortical body maps.

Keywords: central cortex, delta-brush, EEG, fetus, myoclonic twitches

Introduction

Early patterns of correlated neuronal activity play an important role in cortical development by guiding neuronal differentiation, migration, synaptogenesis, and formation of neuronal networks (Van der Loos and Woolsey 1973; Komuro and Rakic 1993; Rakic and Komuro 1995; Katz and Shatz 1996; Ben Ari 2001; Holmes and McCabe 2001; Llinas 2001; Fox 2002; Cang and others 2005; Moody and Bosma 2005). Studies in animal models have revealed that neuronal activity in the developing visual and somatosensory cortical areas is determined by 2 different yet equally important mechanisms: intrinsic oscillations and afferent input. In the visual system, afferent input is provided by spontaneous retinal waves that drive synchronized bursts of activity in the lateral geniculate nucleus and visual cortex in an eye-specific manner (Galli and Maffei 1988; Meister and others 1991; Wong and others 1993; Mooney and others 1996; Weliky and Katz 1999; Chiu and Weliky 2001, 2002; Torborg and Feller 2005; Hanganu and others 2006). In the developing somatosensory cortex, endogenous spindle-burst oscillations are driven in a somatotopic manner by sensory feedback resulting from sporadic muscle twitches that are spontaneously generated in the spinal cord and subcortical structures (Blumberg and Lucas 1994; O'Donovan 1999; Petersson and others 2003; Khazipov and others 2004). Thus, during early postnatal development, both the visual and somatosensory developing systems of altricial animals possess endogenous mechanisms of stimulation that drive intrinsic cortical oscillatory patterns with little need for the environment.

The role of such endogenous mechanisms of sensory stimulation should be even more important in primates. Indeed, both in human and nonhuman primates, extensive development of the somatosensory cortex takes place during the fetal stage (Molliver and others 1973; Rakic and others 1986; Zecevic and Rakic 1991, 2001; Burkhalter and others 1993; Kostovic and Judas 2002). The primate fetus develops in utero in conditions of limited sensory stimulation from the external world, and the source of sensory input to the somatosensory cortex has not been determined. On the other hand, recurrent myoclonic jerks and intermittent oscillatory patterns of cortical activity are present in humans during the fetal developmental stage (Dreyfus-Brisac and Larroche 1971; Hamburger 1975; de Vries and others 1982; Anderson and others 1985; Cioni and Prechtl 1990; Stockard-Pope and others 1992; Prechtl 1997; Lamblin and others 1999; Scher 2006). In keeping with the findings made in the neonatal rat (Khazipov and others 2004), this raises a hypothesis that spontaneous motor activity provides sensory input and drives cortical activity in human fetus.

The dominant pattern of rapid oscillatory activity starting from the sixth month of postconceptional age is delta-brush (Dreyfus-Brisac and Larroche 1971; Anderson and others 1985; Stockard-Pope and others 1992; Lamblin and others 1999; Scher 2006), which has also been described as "spindle-shaped bursts of fast activity" (Ellingson 1958), "rapid rhythm" (Dreyfus-Brisac 1962; Nolte and others 1969; Parmelee and others 1969), "rapid bursts" (Dreyfus-Brisac 1962), "spindle-like fast" (Watanabe and Iwase 1972), "fast activity at 14–24 Hz" (Goldie and others 1971) and "ripples of prematurity" (Engel 1975). A delta-brush consists of 8- to 25-Hz spindle-like, rhythmic activity superimposed on 0.3- to 1.5-Hz delta waves. Delta-brushes are predominantly expressed in central areas before 28 weeks and are then recorded in both central, temporal, frontal, and occipital areas from 28 weeks to near term (Dreyfus-Brisac and Larroche 1971; Anderson and others 1985; Stockard-Pope and others 1992; Lamblin and others 1999; Scher 2006). The prognostic value of background activity and delta-brushes in preterm infants has been well established (Tharp and others 1981; Holmes and Lombroso 1993; Biagioni and others 1994; Scher and others 1996). However, the mechanisms of generation of delta-brushes and the physiological link between delta-brushes and spontaneous motor activity in humans are at present unknown. In the present study, using simultaneous electroencephalography (EEG) and movement recordings from premature human neonates of 29–31 weeks postconceptional age, we provide evidence that sensory feedback resulting from spontaneous hand and foot movements provides somatosensory

cortical stimulation and triggers delta-brushes in the corresponding areas of the somatosensory cortex.

Materials and Methods

The study was performed in 13 premature neonates of 29–31 weeks postconceptional age, 3–7 days after birth at the neonatal intensive care unit at Saint-Vincent de Paul Hospital (Paris, France). Experiments were carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and the experimental protocol was approved by the Ethics Committee of Institut National de la Santé et de la recherché Médicale and by the Commission Nationale Informatique et Liberté. Informed written consent was obtained from the parents. All the neonates were at low neurological risk, including several normal neurological examinations, normal transcranial ultrasonography, and no history of infection and perinatal asphyxia. All the neonates were followed for at least 6 months after birth and have had several normal neurological examinations and showed normal motor development.

Recordings were made in the patients' bed under aseptic conditions required for manipulations of premature neonates and under conventional and stable lighting conditions. Recordings of electrocardiogram (ECG) and respiration were routinely performed. Digital EEG was performed according to the 10/20 international system (Cooper and others 1980) using 9 scalp miniature silver chloride cupules electrodes (10 mm in diameter, 8-mm contact) positioned above the central (C3 and C4), frontal pole (FP1 and FP2), occipital (O3 and O4), and temporal (T3 and T4) cortical areas; FPz electrode served as a reference (Fig. 1*A*, n = 10 neonates). In 3 additional cases, recordings were performed with an additional Cz electrode. The impedance of the recording electrodes was decreased using EEG abrasive skin gel (Nupred) on the scalp and electrolyte gel (Tenzo) on the electrodes before the recording period. Skin impedance was maintained above 10 kΩ during recording at all the recording sites. Signals were amplified (1000×), filtered at 0.16- to 97-Hz bandpass, acquired at 256 Hz using the Deltamed system (France), and analyzed offline using the Coherence 3NT program (Deltamed, France). A base time of 20 s, a time constant of 0.3 s, and a notch of 50 Hz were used during the analysis. Each recording session began approximately at 9–10 AM and lasted for 1 h to obtain data on quiet, indeterminate, active sleep, and awake states. Delta-brushes were present during all behavioral states, but because the movements in awake state were complex and because EEG was strongly artefacted during awake states, we limited analysis to the quiet, active, and indeterminate sleep. The behavioral states of the neonate were determined through visual scoring of EEG, ECG, eye opening, and respiration as previously described (Watanabe 1992; Curzi-Dascalova and others 1993; Curzi-Dascalova and Mirmiran 1996; Lamblin and others 1999). The time spent in various behavioral states was distributed as following (n = 13 neonates): 1) wakefulness, 5.1 ± 0.5 min (irregular, mixed pattern of EEG with frequent artefacts, open and moving eyes, high rate and irregular heart and respiratory patterns); 2) quiet sleep, 3.5 ± 0.5 min (discontinuous EEG, eyes closed, regular respiration, unfrequent jerks, and absence of phasic movements); 3) active sleep, 12 ± 2 min (continuous EEG, eyes closed, irregular respiration, frequent twitches, and phasic jerky movements); and 4) indeterminate sleep, 31 ± 5 min (when the above state criteria were not met). This is in keeping with the results of previous studies suggesting that quiet sleep emerges at 30 weeks postconceptional age with a large amount of time spent in indeterminate sleep and with short awake periods (Mirmiuran and others 2002). In total, 32 ± 4 min of artifact-free recording time was obtained per patient during quiet, active, and indeterminate sleep (n = 13).

The EEG was first analyzed visually by a well-trained neurophysiologist and was considered as normal for the gestational age. The EEG was then analyzed in depth in consecutive 5-s artifact-free epochs. Delta-brushes were detected independently from the video monitoring and movement recordings. Because the delta component of delta-brushes is more diffuse, detection of delta-brushes was based on the rapid oscillatory component in 8- to 25-Hz frequency range. Using automatic detection software based on wavelet analysis (Coherence NT, Deltamed), the rapid oscillatory component of a delta-brush was detected using the following criteria: a wavelet centered on 8–25 Hz, power threshold was set at 20 μV^2, and the duration threshold was >500 ms. Power spectrum analysis was performed using fast Fourier transformation of the automatically detected delta-brushes (Fig. 1) or in 2-s epochs before and after each movement, in order to calculate a normalized power that corresponds to a difference or ratio (specified in the text) between the powers before and after movement.

Movements of the hand and foot were recorded using piezoelectric devices placed at the wrists and ankles as well as by video monitoring. A digital video camera was connected to the EEG acquisition system, and the video was synchronized online with the EEG recording using Coherence software (Deltamed). Movement analysis was independent of EEG. Hand and foot movements were first identified by piezoelectric device recording and were further confirmed by analysis of the video. Myoclonic twitches and brief phasic hand and foot movements were considered for analysis, whereas complex or prolonged movements were discarded and only unilateral isolated hand or foot movements were considered for analysis shown in Figures 3, 5, and 8. Five to fifteen tactile stimulations were performed per patient by gentle caress of the right and left hands or feet (preferentially fingers and palm) mainly during quiet sleep. Stimulations were made directly by hand connected to a contact detector and were recorded concomitantly with EEG (Supplementary video 1).

Results

Basic Characteristics of Delta-Brushes

EEG in the 29–31 weeks postconceptional age preterm neonates during sleep was discontinuous or semidiscontinuous, with bursts of delta activity alternating with periods of hypoactivity (Fig. 1*B*), that is, in keeping with the results of previous studies (Dreyfus-Brisac 1962; Stockard-Pope and others 1992; Lamblin and others 1999; Vanhatalo and others 2002, 2005; Scher 2006). Bursts of delta activity that actually correspond to slower DC shifts and are filtered at 1-Hz highpass filter in the conventional recordings (Vanhatalo and others 2002, 2005) were often synchronous over large cortical areas and even whole brain, particularly during quiet sleep (Fig. 1*B,C*). Bursts of delta activity were often superimposed by spindle-shape alpha–beta oscillations giving rise to the so-called "delta-brush" pattern (Fig. 1*B–D*). In agreement with previous studies (see Introduction), delta-brushes consisted of rapid oscillations at 8–25 Hz (maximum power at 13.5 ± 2.5 Hz [mean ± SE]), lasting 1.4 ± 0.1 s and overriding slow delta waves (0.3–2 Hz) (interevent interval 15 ± 2 s; n = 1231 ± 195 events per recording site in 10 infants, Fig. 1*E*). In addition to the dominant alpha–beta component, delta-brushes also occasionally contained relatively small gamma component (Figs 2*B* and 3*A*). Because the rapid alpha–beta oscillatory component is the most specific feature of the delta-brush pattern, we have further used intermittent oscillations at 8–25 Hz for the detection of delta-brushes. In monopolar recordings, delta-brushes were expressed at all recording sites but tended to be more frequent at central recording sites (maximum of 0.08 ± 0.01 s^{-1} at central electrodes [C3–C4], minimum of 0.06 ± 0.01 s^{-1} at frontal pole electrodes [FP1–FP2], n = 1536–1316 and 1073–973 events, respectively, P = 0.39) (Fig. 1*E*). Comparing the occurrence of delta-brushes at different bipolar derivations, we found that delta-brushes can be correlated over large cortical areas, sometimes over the whole cortex, but can also be spatially confined (Fig. 1*B,F*). It was also noted that central delta-brushes correlated with the hand movements (Fig. 1*B*), and this correlation was explored in the further analysis.

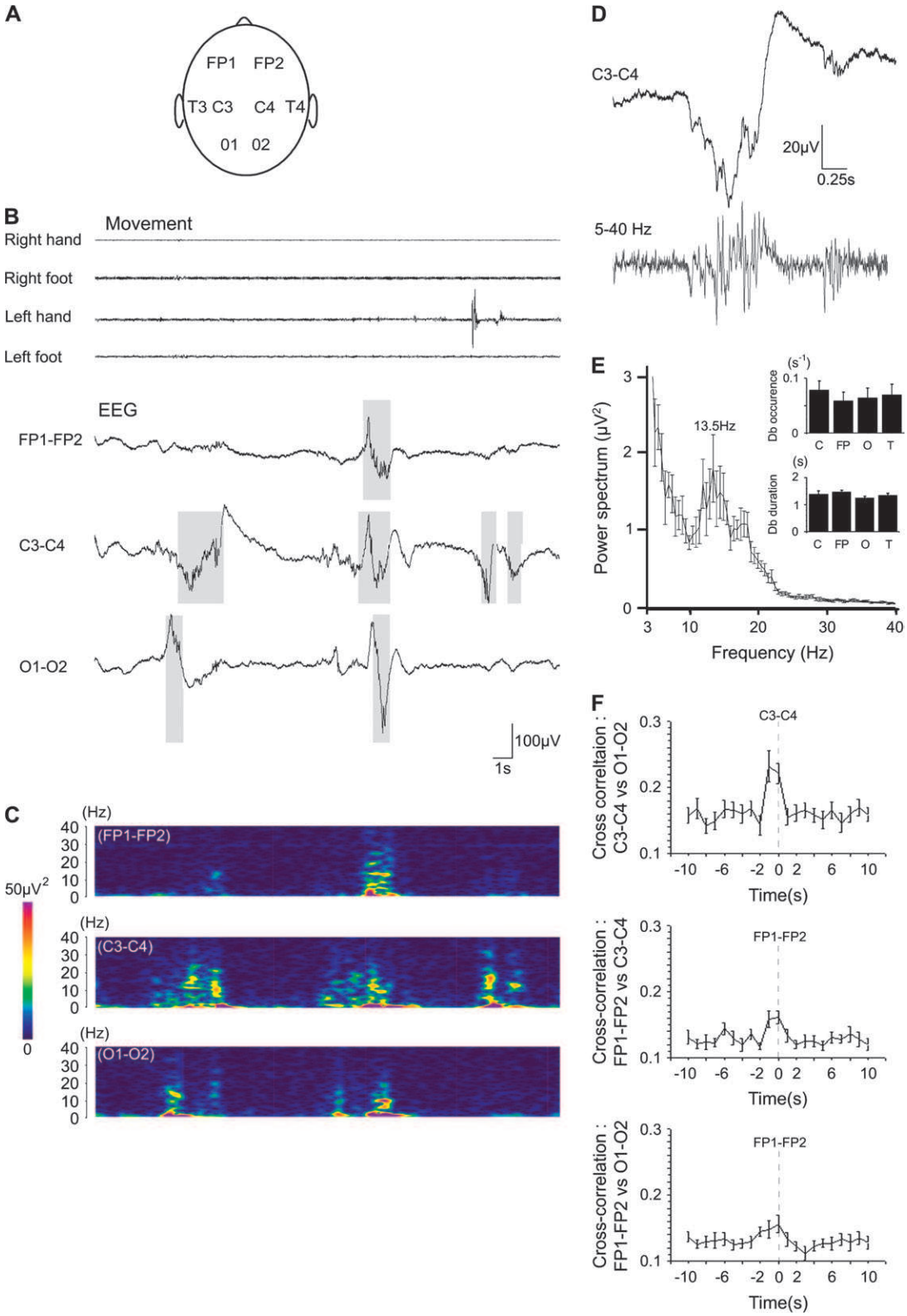

Figure 1. Delta-brushes in human preterm neonates of 29–31 weeks postconceptional age. (*A*) Schematic representation of the 8 electrode placement on the skull. (*B*) Representative example of 3 simultaneous EEG traces recorded in bipolar transversal montage (FP1–FP2, C3–C4, and O1–O2) during quiet sleep in a 30 weeks postconceptional age neonate. Bursts of delta waves alternate with periods of hypoactivity. Delta-brushes are characterized by alpha–beta oscillations superimposed on delta waves (gray squares). Traces above show concomitant hand and foot movement recordings. (*C*) Wavelet analysis of bipolar EEG recordings shown in (*B*). (*D*) Example of a delta-brush on expanded time scale: raw trace (top) and bandpass filtered 5–40 Hz (bottom). (*E*) Average power spectrum of delta-brushes recorded from all 8 recording sites. Insets: average occurrence and duration of delta-brushes at central (C), frontal (FP), occipital (O), and temporal (T) electrodes (n = 9842 delta-brushes, pooled data of monopolar recordings from 10 neonates). (*F*) Normalized cross-correlograms between central and occipital, central and frontal, and frontal and occipital delta-brushes recorded in bipolar transversal montage. Pooled data from 10 neonates.

Central C3/C4 Delta-Brushes Correlate with Hand Movements

In order to test the relationship between movements and delta-brushes in the somatosensory cortex, we analyzed the correlation between hand movements and electrical activity at central electrodes (C3 and C4). These electrodes are the closest to the hand representation area in the somatosensory cortex as evidenced by the maximal response to median nerve and tactile hand stimulation (Smit and others 2000; Pihko and others 2004). Delta-brush intermittent oscillatory activity was first analyzed using bipolar montage between the left and right central electrodes that shows delta-brushes independently of the reference electrode and of the side of their origin (Fig. 2*A*). Simultaneous video recordings and monitoring of hand movements (including unilateral and bilateral hand movements) using piezoelectric movement detectors placed at the wrists revealed a robust temporal correlation between hand movements and C3–C4 delta-brushes, with the motor activity preceding cortical events (Fig. 2; Supplementary video 2). Two types of analysis of the relationship between the movements and delta-brushes were performed: 1) cross-correlation analysis between the hand movements and C3–C4 delta-brushes and 2) comparative power spectrum analysis of the activity at C3 and C4 electrodes during the 2-s epochs preceding and following each movement. Cumulative analysis of the hand movements and delta-brushes revealed that the great majority of hand movements (86 ± 2%; n = 530) were followed by one or more delta-brushes within a 2-s period (Fig. 2*D*, average delay: 242 ± 42 ms, n = 2084 C3–C4 delta-brushes recorded in bipolar montage in 10 patients) and that 29 ± 2% (n = 2084) of C3–C4 delta-brushes were preceded by the hand movements within a 2-s period. In general, there was a 12 ± 4 fold increase in the probability of C3/C4 delta-brush occurring during the 2-s time window following hand movements (n = 10 neonates). Power spectrum analysis of EEG activity in C3 and C4 electrodes revealed a significant increase in the power of frequencies characteristic of delta-brushes following hand movements (6.2 ± 0.7 fold increase at 17 Hz; 4.0 ± 0.9 fold increase at 1 Hz, $P < 0.01$; n = 530 movements in 10 neonates; Fig. 2*E*).

Although the dependence on the behavioral state was not analyzed in detail, we noticed that during quiet sleep, the proportion of C3–C4 delta-brushes that were preceded by a hand movement (12 ± 2%) was significantly less than the average sleep value (29 ± 2%; $P < 0.05$, n = 10 neonates). Movement-related delta-brushes could also be seen during awake state (not shown), but statistical analysis during the awake state

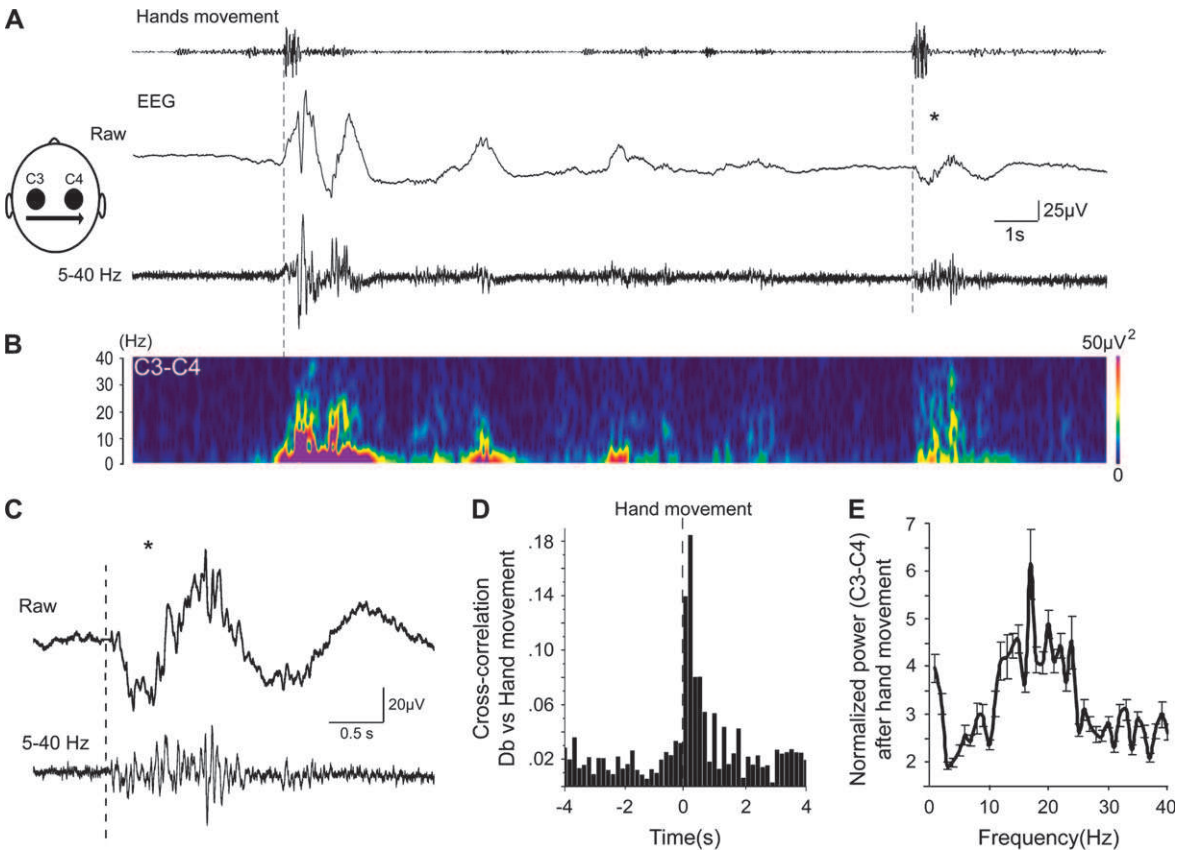

Figure 2. Spontaneous hand movements trigger C3–C4 delta-brushes in human premature somatosensory cortex. (*A*) Simultaneous recordings of hand movements (upper trace) and bipolar C3–C4 recordings from central regions, which correspond to hand representation in the somatosensory cortex at wide band (middle trace) and filtered at 5- to 40-Hz bandpass (lower trace). Note delta-brushes following hand movements. Recordings from a 30 weeks postconceptional age neonate. (*B*) Wavelet analysis of the trace above. (*C*) An example of the movement-associated delta-brush on an expanded time scale. The onset of hand movement is indicated by dashed line. Note that rapid activity is nested in the envelope of a slow delta oscillation. (*D*) Cross-correlogram between hand movements and C3–C4 delta-brushes. Onset of hand movement served as a reference (t = 0); onset of the rapid component (8–25 Hz) was taken as the time of C3–C4 delta-brushes (pooled data from 10 neonates; 493 hand movements; 765 delta-brushes). (*E*) Average power spectrum of the hand movement–associated activity recorded at C3–C4 electrodes. The power spectrum of a 2-s time window after the beginning of movement is normalized to the power spectrum obtained during the 2-s period preceding each movement. Pooled data from 10 neonates of 29–31 weeks postconceptional age.

could not be performed because of frequent movement and electromyogramm (EMG) artefacts (Lamblin and others 1999).

Contralateral Predominance of C3 and C4 Delta-Brushes Following Hand Movements

The correlation between cortical activity and movement may reflect an overall increase in the level of excitation in the nervous system, such as that which occurs during arousal from sleep (Crowell and others 2004). Alternatively, proprioceptive and tactile sensory feedback associated with movement may trigger the delta-brushes specifically, as has been described in the neonatal rat (Khazipov and others 2004). If the latter hypothesis is correct, the spatial organization of the cortical activity that follows spontaneous movements should correspond

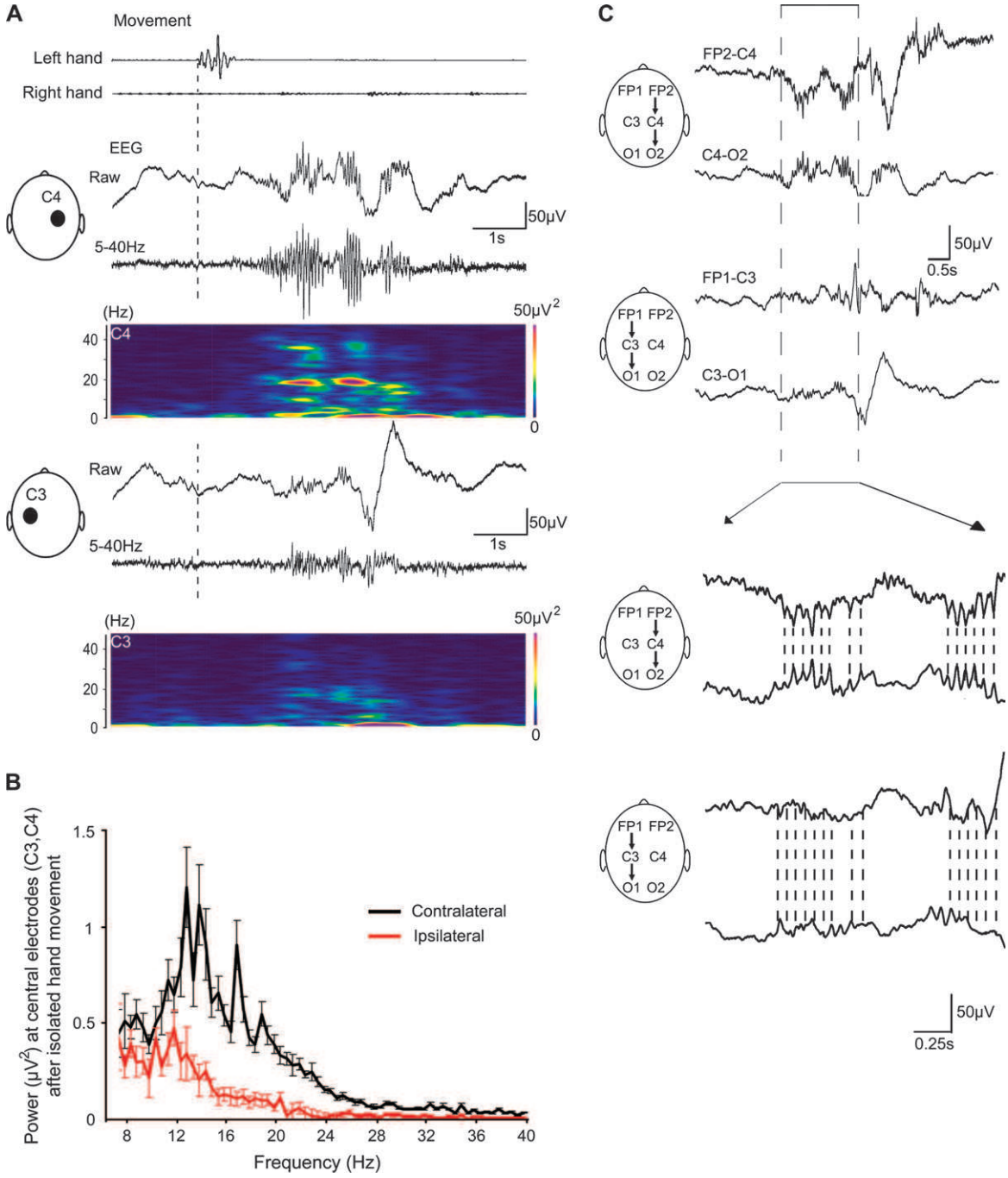

Figure 3. Contralateral dominance of the hand movement–associated cortical C3/C4 delta-brushes. (*A*) An isolated myoclonic jerk of the left hand is followed by a delta-brush in the contralateral right central region (C4). In the ipsilateral left central region (C3), the fast cortical activity is much smaller in amplitude. Recordings from a 30 weeks conceptional age neonate. (*B*) Average power spectrum of the contralateral (black line) and ipsilateral (red line) activity at C3 and C4 electrodes associated with isolated unilateral hand movements. Power spectrum of the 2-s period before the beginning of movement is subtracted from the power spectrum obtained during the 2-s period following movement. Pooled data from 10 neonates of 29–31 weeks postconceptional age (total of 120 isolated hand movements). (*C*) Bipolar montages of the event shown on (*A*) from the right hemisphere (FP2–C4 and C4–O2) and from the left hemisphere (FP1–C3 and C3–O1) show phase reversal of both delta and fast activity at the C4 electrode that is placed above the left-hand representation in the somatosensory cortex. Rapid oscillations are shown on the expanded time scale below; dashed lines indicate phases of the fast oscillations.

to the anatomy of the somatosensory pathways. Because the principal somatosensory pathways convey tactile and proprioceptive information contralaterally, we compared the occurrence of delta-brushes between the 2 central regions C3 and C4 analyzed using monopolar montage (Fig. 3). Virtually, all (92%) isolated unilateral hand movements were followed by delta-brushes at electrodes C3 or C4 (Fig. 3*A,B*) within a 2-s period (n = 120 unilateral movements). Bipolar longitudinal recording montage to localize the side of activity (Ettinger and others 2006) revealed phase reversal of the rapid oscillations associated with the delta-brushes at the contralateral central electrodes (Fig. 3*C*). When responses were seen in the ipsilateral somatosensory cortex, they always occurred coincident with a rapid oscillation in the contralateral cortex and were significantly smaller in amplitude (normalized amplitude: 0.8 ± 0.1 μV^2 and 0.3 ± 0.1 μV^2 power at 15 Hz in the contralateral and ipsilateral sides, respectively; n = 120 epochs in 10 patients; P = 0.012) (Fig. 3*B*). Taken together, these results suggest that delta-brushes associated with hand movements are predominantly generated in the contralateral C3/C4 central cortical areas. However, rapid activity in the ipsilateral cortex may reflect not only passive propagation from the contralateral source but also interhemispheric propagation of activity via transcalosal fibers or transmission of the sensory feedback via ipsilateral somatosensory pathway (Erberich and others 2006).

Topography of Delta-Brushes Correlated with Hand Movements

To further determine the cortical topography of rapid oscillations associated with hand movements, we compared the relationship between isolated unilateral hand movements and the activity recorded from the central (C3 and C4), frontal pole (FP1 and FP2), occipital (O1 and O2), and temporal (T3 and T4) electrodes in a monopolar montage (Figs 4 and 5). Analysis of delta-brushes at each recording site revealed that in contrast to central delta-brushes, delta-brushes in occipital, temporal, and frontal recordings did not significantly correlate with hand movements (Fig. 5*A*, n = 9842 delta-brushes in 10 neonates). The normalized power spectrum at contralateral central electrodes after isolated hand movements (n = 120) revealed a significant enhancement in the power at the central contralateral electrode. This enhancement was maximal at 0–1.5 Hz (P = 0.02) and 8–25 Hz (P = 0.002) and peaked at 17.5 ± 2.4 Hz (Fig. 5*B*). Comparing the increase in the power at 8–25 Hz between different recording sites, we found the maximal increase at C3 and C4 electrodes contralateral to the movements (5.4 ± 1.3 and 4.2 ± 0.8 fold increase, n = 45 and n = 75 isolated movements of the right and left hand, respectively, P < 0.0001, n = 10 neonates). The power increase was significantly greater than the average increase at the rest of the 7 electrodes (1.9 ± 0.1 fold increase; P < 0.05; Fig. 5*C*). Two-dimensional power spectrum analysis at 8–25 Hz of the 2-s epoch that follows hand movement revealed the central contralateral predominance of the delta-brushes (Fig. 5*D*). It should be noted that because of the limited number of recording sites, the size of the activated areas was likely overestimated and the actual size of the activated areas was smaller.

Direct Hand Stimulation Triggers Contralateral C3 and C4 Delta-Brushes

The spatiotemporal correlation between spontaneous hand movements and delta-brush oscillations in the central cortex suggests that they could be triggered by the movement-associated sensory activation. If this hypothesis is correct, direct sensory stimulation of the hands should also trigger delta-brushes. Indeed, gentle caress of premature infants' hands during quiet and indeterminate sleep reliably (with 83 ± 4% probability) evoked delta-brushes with a maximal power at the contralateral central recording sites (Supplementary video 1, Figs 6 and 7; average duration of tactile stimulations: 511 ± 140 ms, n = 152 hand stimulations in 10 neonates). The most efficient trigger was stimulation of the palm, which is in keeping with it having the largest cortical representation in the somatosensory cortex (Penfield and Rasmussen 1950). Cross-correlation analysis revealed a strong correlation between hand stimulations and contralateral delta-brushes, with an average latency of 292 ± 51 ms (Fig. 7*A*, n = 152 stimulations in 10 neonates). The properties of delta-brushes evoked by tactile hand stimulation were not significantly different from those observed following spontaneous hand movements (maximum power at 17 ± 3 Hz, average duration 1.2 ± 0.1 s; n = 152 events in 10 infants); the delta component was also prominent in the stimulation-evoked delta-brushes (Figs 6 and 7*C,D*). Power spectrum analysis of EEG activity at the 8 electrodes revealed a significant increase in the power of the alpha–beta component at the contralateral central electrode following hand movements (7.1 ± 1.0 fold increase at 17 Hz; n = 152 stimulations in 10 infants; P < 0.001; Fig. 7*B,C*). Thus, delta-brushes in central C3/C4 areas in human premature neonate can be triggered via the direct tactile hand stimulation.

Feet Movements and Stimulations Trigger Cz Delta-Brushes

In the next experiment, we recorded 3 preterm infants (30 weeks of gestational age) with an additional ninth electrode located at central median recording site Cz according to the 10/20 international system (Fig. 8*A*) (Cooper and others 1980). In this configuration, Cz delta-brushes differed neither in frequency of occurrence (0.05 ± 0.02 s^{-1}) nor in duration (1.2 ± 0.3 s) from delta-brushes at other recording sites (n = 251 delta-brushes in 3 neonates, Fig. 8*B*). Power spectrum analysis of the activity recorded at Cz revealed strong enhancement at alpha–beta frequency after isolated foot movement (n = 39 isolated movement of left or right foot in 3 neonates, Fig. 8*C*). There was a robust correlation between Cz delta-brushes and movements of the left or right foot, with the movements preceding delta-brushes by 336 ± 150 ms (n = 251 delta-brushes and 39 movements in 3 neonates, Fig. 8*D*). Direct tactile stimulation of the left or right foot reliably evoked Cz delta-brushes (delay = 288 ± 40 ms; n = 23 stimulations in 3 neonates, Fig. 8*E* and Supplementary Video 3), and this was associated with a strong enhancement of power at the delta and rapid frequencies (Fig. 8*F*). In the same neonate, 2-dimensional analysis revealed central median and central lateral (Fig. 8*G*) compartmentalization of the increase in the power at alpha–beta frequency following foot (n = 23) and hand (n = 25) stimulations (n = 3 neonates). Thus, hand and foot movements or stimulation specifically trigger delta-brushes at the central lateral (C3 and C4) and central median (Cz) recording sites, respectively.

Discussion

In the present study, we provide evidence that during the fetal stage of human development, spontaneous movements provide,

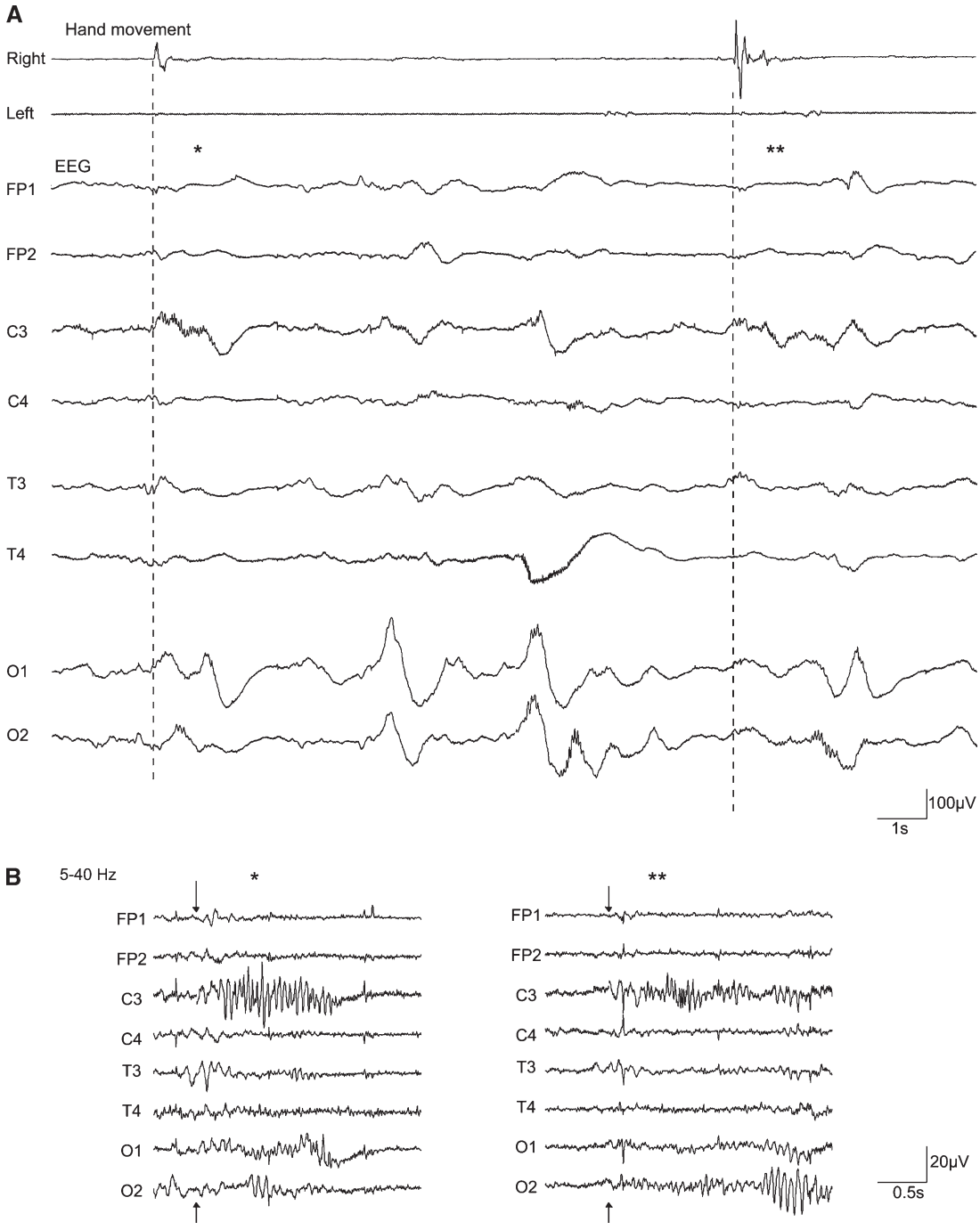

Figure 4. Topography of the movement-triggered delta-brushes: representative example. (*A*) Simultaneous recordings of the hand movements and monopolar recordings from the 8 recording sites (reference: FPz). Note that 2 consecutive twitches of the right hand (their onset is indicated by dashed lines) are followed by delta-brushes at the contralateral central electrode (C3). (*B*) Corresponding to the movements filtered traces (bandpass 5–40 Hz) on expanded time scale (arrows indicate the onset of movements). Note that delta-brushes are also present in visual (O1 and O2), temporal (T3 and T4), frontal (FP1 and FP2), and ipsilateral central (C4) cortex, but they do not correlate with the right-hand movements.

via feedback signaling, sensory stimulation and trigger delta-brushes in the developing somatosensory cortex in a somatotopic manner. Our findings indicate an important role of spontaneous motor activity for somatosensory cortical stimulation during fetal development and shed light on the origin and possible physiological roles of delta-brushes, a dominant pattern of cortical activity during the third trimester of gestation.

Our conclusion that there is a link between movement and delta-brushes is based on the following 2 principal observations: 1) hand and foot movements were typically followed by delta-brushes in the contralateral hand and foot representation areas in the somatosensory cortex and 2) direct hand and foot stimulation reliably evoked delta-brushes in the corresponding cortical areas. The delay of delta-brushes after movements

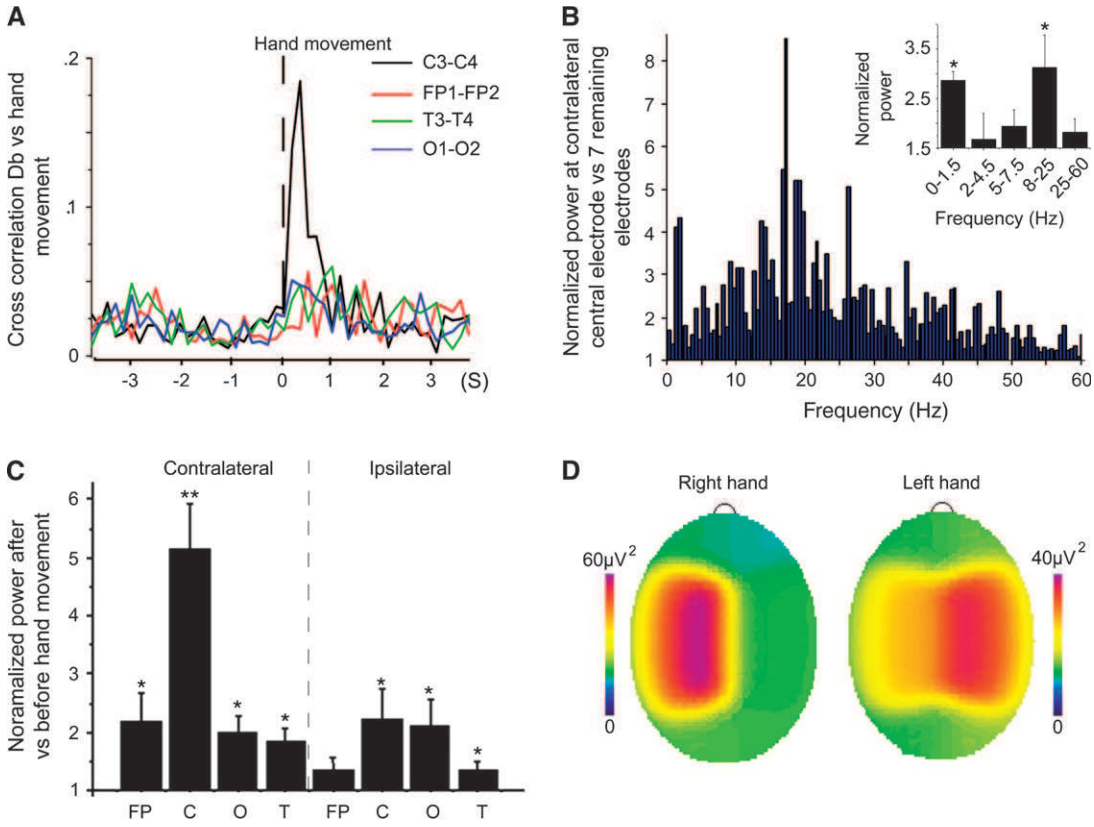

Figure 5. Statistics on the topography of the movement-triggered delta-brushes. (*A*) Normalized cross-correlograms between hand movements and delta-brushes in monopolar recordings from central lateral (black), frontal pole (red), temporal (green), and occipital (blue) cortex (n = 2853, 2041, 2697, and 2251 delta-brushes, respectively, 120 isolated hand movements; pooled data from 10 neonates). (*B*) Power spectrum of the hand movement–triggered activity at the contralateral central electrodes normalized to the remaining 7 electrodes (n = 120 hand twitches; pooled data from 10 neonates). Inset: power spectrum of the hand movement–triggered activity at the central electrodes normalized to the remaining 7 electrodes in different frequency bands; note that power increase is maximal at 0–1.5 and 8–25 Hz; * indicates $P < 0.05$. (*C*) Normalized power of cortical activity at 8–25 Hz triggered by isolated right- and left-hand movements at different cortical recording sites. The movement–triggered increase in alpha–beta power is maximal at the contaralateral central recording sites (n = 120 unilateral hand twitches; pooled data for C3 and C4 recordings from 10 neonates; * indicates $P < 0.05$ and ** indicates $P < 0.0001$). (*D*) Two-dimensional maps of the power of fast cortical activity triggered by isolated hand twitches (average of 21 twitches; neonate of 31 weeks postconceptional age).

and stimulation was variable and relatively long, in the range of hundreds of milliseconds, which is significantly longer than the delay of the evoked somatosensory potentials (about 70 ms for the hand and foot at 31 weeks [Pike and others 1997; Pihko and Lauronen 2004]). Interestingly, similar delays for both the sensory-evoked potentials and spindle bursts, which are homologous to delta-brushes (Khazipov and Luhmann 2006), have also been reported in the newborn rats (Khazipov and others 2004). These findings are consistent with the idea that delta-brushes are endogenous cortical network-driven events that can be triggered by sensory input. Similar to other types of network-driven activities (e.g., giant depolarizing potentials in the hippocampus (Ben-Ari and others 1989), the delta-brushes display long and variable delays after stimulation.

Analysis of the spatial distribution of the rapid oscillations associated with delta-brushes revealed activation of large cortical areas significantly exceeding the presumed hand and foot representation in somatosensory cortex (Figs 5, 7, and 8). This can be due to 1) the spread of delta-brushes beyond the activated areas (Fig. 1) that has been also observed in the neonatal rat (Khazipov and others 2004), 2) an overall increase in the level of excitation in the nervous system associated with the movement and stimulation, and 3) limited spatial resolution of the recordings—due to a limited number of recording sites in a small premature neonate's head—that could result in an error of the estimation of the real size of the cortical areas activated during delta-brushes. Using recording systems with larger number of electrodes should enable one to overcome the latter technical problem and will provide better spatial resolution of the cortical areas activated during delta-brushes. On the other hand, reliable correlation between the hand and foot movements/stimulation and delta-brushes at C3, C4, and Cz electrodes in a configuration currently used in clinics may be of interest as a potential diagnostic/prognostic tool.

Several patterns of intermittent correlated activity have been described in the developing cortex of animal models. Neuronal domains synchronized via gap junctions (Yuste and others 1992, 1995; Kandler and Katz 1995, 1998), waves (Peinado 2000, 2001), acetylcholine-dependent alpha/beta/gamma oscillations (Dupont and others 2006), and early network oscillations driven by intracortical glutamatergic and excitatory GABAergic connections (Garaschuk and others 2000) have all been described in the neonatal rodent neocortical slices in vitro. Correlated neuronal activity was also observed in neonatal somatosensory cortex in the intact hemisphere preparation in vitro (Dupont and others 2006). In the neonatal rat in vivo, the only electrical pattern of synchronized neuronal activity that has been described at present in the neocortex is a spindle burst (Khazipov and others 2004). The similar spindle-shape and oscillatory frequency, local nature, correlation with movements, ability to

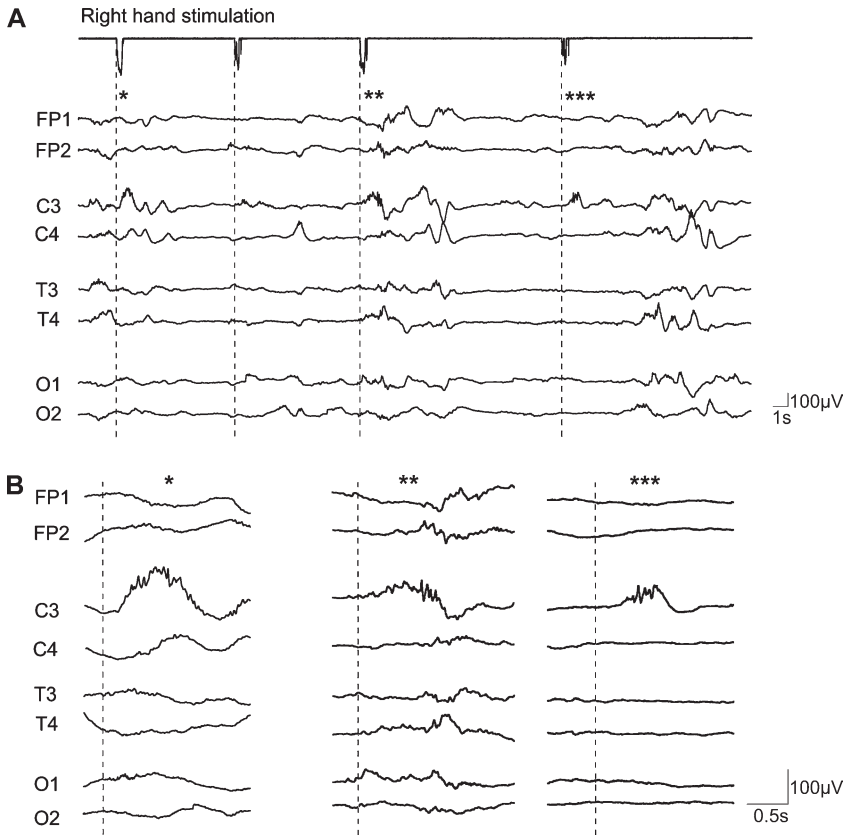

Figure 6. Sensory stimulation of the hand evokes contralateral central delta-brushes. (*A*) Simultaneous recordings of hand stimulation and monopolar recordings from the 8 recording sites (average as reference). Note that caressing the neonate's right hand (indicated by dashed line) reliably evokes delta-brushes in the left central region (C3). (*B*) Three examples of the stimulation-evoked delta-brushes marked by asterisks on panel A are shown on expanded time scale (dashed lines indicate the onset of stimulations). Wide-band (0.16–97 Hz) recordings from 30 weeks postconceptional age neonate.

be evoked by tactile stimulation, and occurrence within comparable developmental windows indicates that spindle bursts observed in the rat (Khazipov and others 2004) are homologous to human delta-brushes (Khazipov and Luhmann 2006). Several lines of evidence indicate that the delta-brush is an endogenous network pattern that can also be triggered in natural conditions by the sensory feedback resulting from movements: 1) nearly two-thirds of delta-brushes in the somatosensory cortex of human premature neonates occurred in the absence of overt movements, 2) S1 spindle bursts in the neonatal rats persist after sensory deafferentation (Khazipov and others 2004), and 3) spindle-shape oscillations reminiscent of delta-brushes can be generated in the neonatal rodent isolated cortex and cortical slices (Dupont and others 2006).

The great majority (86%) of hand movements were followed by delta-brushes, and a nearly similar rate was found for the direct hand stimulation–evoked delta-brushes (83%). In the neonatal rat, spindle-burst failures occur when the sensory input concurs with the ongoing activity (Khazipov and others 2004). This suggests that failures in the movement/stimulation-triggered delta-brushes are rather due to the refractory periods in cortical excitability following delta-brushes. In keeping with this hypothesis, we found that the failure rate increases during the periods of continuous activity during active sleep.

We found that at 29–31 weeks postconceptional age, the behavioral states and corresponding differentiation of EEG start to emerge. At this point, most of the time is spent in "indeterminate," sleep (Mirmiran and others 2002). A correlation between movement and delta-brushes was observed during all types of sleep. Interestingly, during quiet sleep, in which the neonates spent ~5% of the time and during which spontaneous movements were rare, the proportion of spontaneous (i.e., nonpreceded by movement) delta-brushes was significantly higher. This is in keeping with the idea that the delta-brush is an endogenous pattern that can be triggered by, but does not necessarily require, sensory input (Khazipov and others 2004). Epochs of waking were rare and short and were associated with frequent artefacts and complex movements (Lamblin and others 1999). Although movement-triggered delta-brushes were occasionally observed during epochs of awaking, detailed analysis of the correlation between movements and delta-brushes could not be performed because movement were complex and associated with movement and EMG artefacts. In future studies, it will be of interest to determine the correlation between movements and delta-brushes during different behavioral states at older developmental stages (>32–34 weeks postconceptional age), when the behavioral states become well differentiated (Lamblin and others 1999). It will also be of interest to determine whether delta-brushes persist and whether their properties are modified in the paralyzed premature neonates under artificial ventilation. This clinical setting eliminates all motor activity and therefore can be particularly useful in determining the level of spontaneous delta-brush activity as well as for studying the tactile-evoked delta-brushes

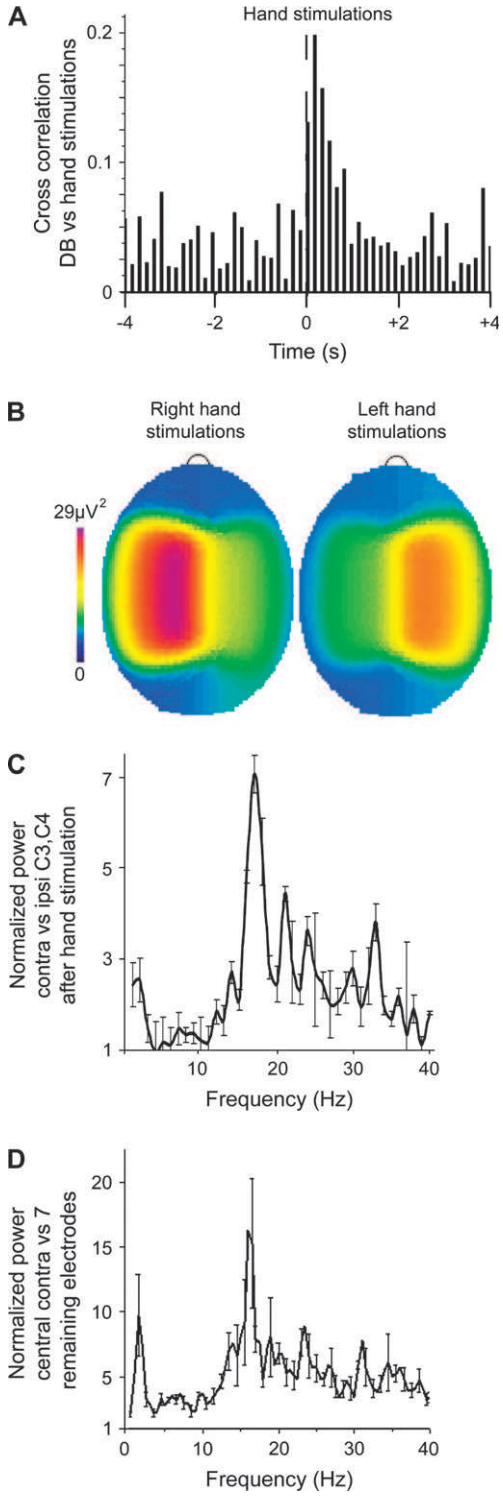

Figure 7. Topography of the delta-brushes evoked by hand stimulation. (*A*) Cross-correlogram between hand stimulations and delta-brushes in the contralateral C3 and C4 electrodes. Onset of hand stimulation served as a reference (t = 0); onset of the rapid component (8–25 Hz) was taken as the time of delta-brush (152 hand stimulations; 2853 C3/C4 delta-brushes; pooled data from 10 neonates). (*B*) Cortical map of the responses evoked by right- and left-hand stimulation presented as alpha–beta power. Note that stimulation-evoked alpha–beta oscillations are predominant in the contralateral cortical areas. (*C*, *D*) Ratios of the normalized power spectra evoked by hand stimulation at central recording sites: (*C*) contralateral versus ipsilateral and (*D*) contralateral versus 7 other electrodes. Data for the left and right hands are pooled together (n = 152 stimulations; 10 neonates).

under conditions preventing muscle responses to the tactile stimulation.

The relevance of our findings to the fetus in utero is presently unknown. However, because brain activity and motor behavior are similar in the fetus and in age-matched premature neonates (Lamblin and others 1999; Rose and Eswaran 2004), it is likely that the present findings can be approximated to the fetus in utero. Our findings may be particularly relevant to the proprioceptive feedback mediated by spindle fibers, in which case the in utero and ex utero conditions might be similar. Tactile feedback from the movements occurring in the context of a neonate lying on bedding materials that will offer considerable friction during movements is clearly different from that resulting from the fetal movements occurring in amniotic fluid. On the other hand, during the third trimester of gestation, the fetus tightly embeds in the uterus and mothers experience fetal movements. This implies that the fetus actually touches the uterus which would provide a tactile signal to the fetus. Thus, it is likely that both proprioceptive and tactile sensory feedback can be produced by fetal movements in utero.

The delta-brush pattern can have multiple physiological roles in the developing cortex, including many aspects of neuronal differentiation and formation of neuronal networks (see Introduction). In humans, extensive development of thalamocortical and intracortical connections takes place during the fetal stage of development (Molliver and others 1973; Burkhalter and others 1993; Kostovic and Judas 2002). Although studies in animal models have demonstrated that the initial configuration of synaptic connections is precise (Bureau and others 2004), it is also well established that activity plays an important role in maintenance and refinement of connectivity (Van der Loos and Woolsey 1973; Katz and Shatz 1996; Holmes and McCabe 2001; Fox 2002). However, the human fetus develops in utero in conditions of limited sensory input from the external world, and the source of sensory input to somatosensory cortex remained unknown. Based on the results of the present study, we propose that sensory feedback resulting from spontaneous fetal movements stimulates specific pattern of cortical activity. This endogenous mechanism of cortical stimulation may be critical for activity-dependent plasticity in the somatosensory pathways and development of the somatosensory cortex during fetal development (Feldman and others 1999; Fox 2002; Petersson and others 2003). This is supported by clinical findings indicating that the properties of fetal or premature motor activity predict neurological and behavioral outcome (Prechtl 1997). Similar principles may also operate in other sensory systems. Indeed, delta-brushes are also present in the occipital cortex (Stockard-Pope and others 1992; Lamblin and others 1999; Scher 2006) (see also Figs 1 and 4) during the developmental window when, according to the studies in rodents, spontaneous waves of activity are generated in the retina (Galli and Maffei 1988; Meister and others 1991; Wong and others 1993; Torborg and Feller 2005) and propagate via the thalamus to the visual cortex (Mooney and others 1996; Weliky and Katz 1999; Chiu and Weliky 2001, 2002; Hanganu and others 2006). This raises a hypothesis that in primates in utero, the occipital delta-brushes driven by the retinal waves could contribute to the development of visual system before visual experience (Rakic 1976). Future studies specifically examining the association of peripheral and cortical activity during fetal development will be required to address this hypothesis in the visual as well as in other sensory systems.

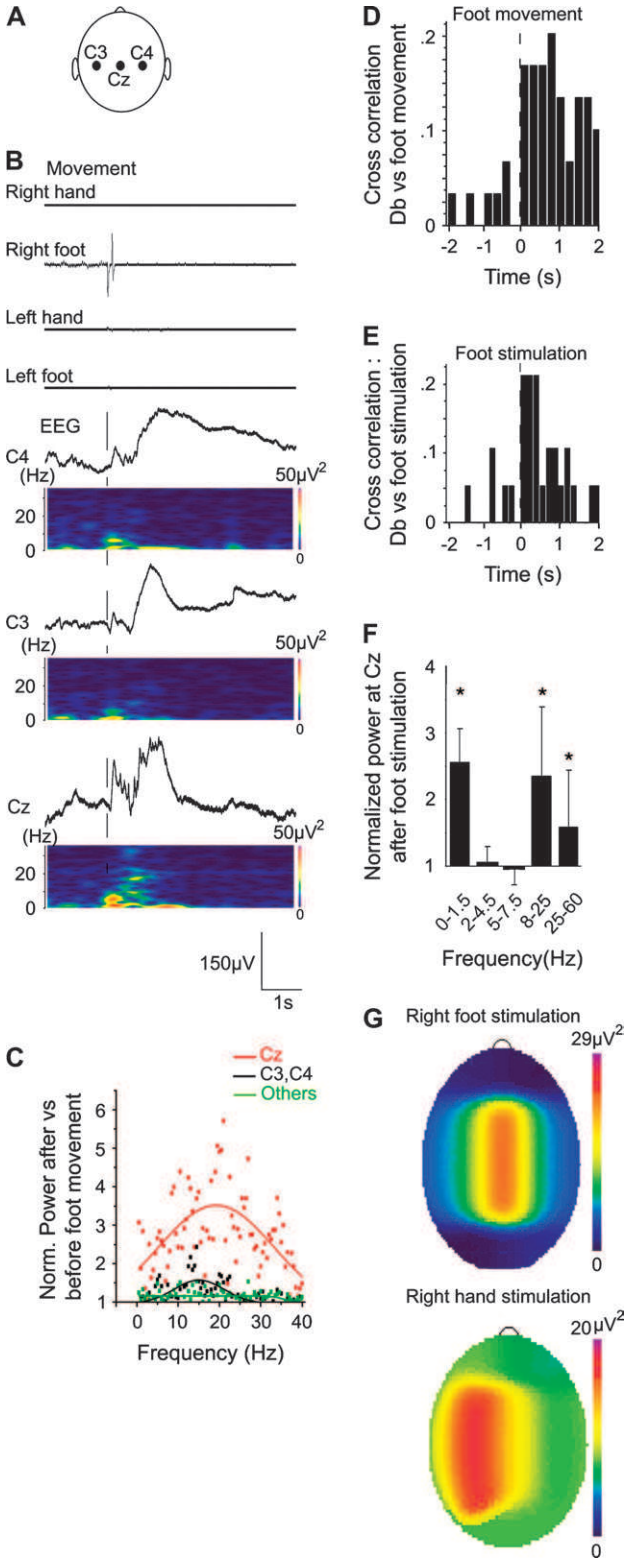

Figure 8. Spontaneous movements and stimulation of the foot evoke central medial Cz delta-brushes. (*A*) Central median position of Cz electrode above the feet representations in the paracentral lobule. (*B*) Simultaneous recording of the right and left feet and hand movements and monopolar EEG at central medial Cz and central lateral (C3–C4) sites. Isolated movement of the right foot is followed by delta-brush at Cz but not at C3 or C4. (*C*) Average power spectrum of the foot movement–associated cortical activity pooled from 3 neonates of 30 weeks postconceptional age. Ratio of the power spectrum of a 2-s time period after the beginning of movement to the power spectrum obtained during the 2-s period preceding each movement (n = 39 foot movements). (*D*) Cross-correlogram between delta-brushes at Cz and foot movements (pooled data from 3 patients, n = 39 isolated foot movement and 251 delta-brushes). (*E*) Cross-correlogram between Cz delta-brushes and foot stimulation (pooled data from 3 patients, n = 23 foot stimulations and 251 delta-brushes). (*F*) Normalized power spectrum after foot stimulations (n = 23). Power spectrum at Cz electrode is normalized to the average power spectrum recorded at the 8 other electrodes (n = 23 stimulations in 3 neonates; * indicates $P < 0.05$). (*G*) Cortical maps of the responses evoked by right and left foot (top) and right-hand (bottom) stimulation presented as a power at alpha–beta band (average of 9 foot and 9 hand stimulations; 30 weeks postconceptional age neonate).

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes

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